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▶ To cite this version:

Anne Branciard. France's search for institutional schemes to promote innovation : the case of genomics: Workshop Innovation, Industry and Institutions in France, Feb. 28-29, 2000Paris, CEPREMAP. 2000. halshs-00098134

HAL Id: halshs-00098134
https://shs.hal.science/halshs-00098134

Preprint submitted on 24 Sep 2006

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France's search for institutional schemes to promote innovation: the case of genomics.

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Workshop Innovation, Industry and Institutions in France, Feb. 28-29, 2000

Paris, CEPREMAP

(first draft)

Biotechnologies represent a typical case of generic technology with high scientific content that spreads throughout a large part of the production system.[1] Their development is thus a major stake in international competitiveness. They offer a privileged domain for the application of Kline and Rosenberg's model of innovation loops, which highlights the two-way connections between the S&T arena and industry. In the life sciences, the technological and R&D aspects are located both upstream and downstream in relation to research: upstream for the use of organisms or living components to analytical ends, or for the perfection of biological research instruments (automation, computer science, detectors, biological and medical engineering, etc.), and downstream through biotechnological applications resulting from advances in scientific knowledge or the industrial development of innovative equipment and procedures contributing to scientific production.

The mastery of the development of biotechnologies entails transformations in the organisation of scientific production which are related to several different dimensions that are now combining to determine their evolution :

- The need for a multidisciplinary combination of knowledge and skills;
- The increasing returns on the recourse to biotechnological knowledge, where the most recent discoveries do not replace the old ones but combine with and systematise them;

[1]. The term *biotechnologies* is used here in the sense of the utilisation of molecules or living organisms for technologies with industrial applications and/or the development of technologies devoted to the study of living things.

- Changes in the production methods of biological science (automation, computerisation), which lead to an increasing methodological codification (catalogues) of biological elements, thus permitting responses to specific demands;
- The considerable proximity between fundamental knowledge and a wide range of innovative industrial applications (agrochemical, pharmaceutical, or environmental), which are gradually coming to light. In fact, biotechnologies are rooted in the academic milieu while interacting with the industrial milieu. They thus constitute a crossroads between one world whose rationale is supposed to be the preservation of diversity and another whose rationale is standardisation. In economic terms, the systematisation of biological knowledge can permit very specialised supply zones to expand, generally through academic spin-offs, while also allowing industrial groups seeking economies of scale to homogenise their production through biology's "new direction".

This tension between the tendency towards standardisation and a preservation of diversification (the research-biotechnologies-industry linkage) is controlled by the forms of interaction between public action schemes rooted in institutional frameworks and new configurations of players composed of laboratories, universities, facilities and firms, which may be organised in networks and/or physically localised.

The elaboration of scientific knowledge and practices about living organisms and their transfer into marketable technology are situated in a specific institutional context, the effectiveness of which depends on the forms of linkage between the scientific research system and the other components of the innovation system (Amable, Barré, Boyer 1997).
The aim of our research on innovation in genomics and biomedical related biotechnologies was to study this phenomenon in the French societal context : first of all for the 1985-1996 decade, which marked the pioneering phase of contemporary molecular biology, its biotechnological tools and its biomedical applications, and then for a second phase of institutional reforms, after 1996. We shall demonstrate that this decade, in spite of its apparent ineffectiveness in the science-innovation tandem (part 1), nonetheless offered the prerequisites for a new technological policy of integration between public and private research and industry (part 2), as exemplified by the creation of an international center for research and development in genomics and biotechnologies in Evry. Within this framework, the first section (1.1.) describes the creation of a scientific and technical arena for genomics, initiated, as is standard

practice in France, by government action. This effort, which was short term and sporadic, nonetheless drew its effectiveness from the fact that it was reinforced by the preponderant impetus of a private player from the non-profit sector. The second section (1.2.) argues that, as in Germany (Casper 1999), the weakness of the biotechnologies sector in France is a consequence of the institutional frameworks created by the public authorities and the strategies of industrial groups. The third section (2.1.) traces the emergence in France of an "ideal model" of research-innovation linkage, tied to the interdependency and diffusion of scientific and technical advances and to the organisational learnings emerging from globalisation. The fourth section (2.2.) analyses the successive institutional reforms, whose implementation is shaped by the societal appropriation of the "model" according to existing French institutional features.

1 1985-1996 : THE CREATION OF A SCIENTIFIC AND TECHNICAL SPACE FOR GENOMICS, BUT NOT A SPACE FOR INNOVATION

In 1985, the launching of the Human Gene (HG) sequencing project in the United States (followed in 1988 on the international level by the organisation HUGO) gave rise to polemics in France and brought out cleavages within the scientific community between fundamental biology, which studies the functioning of genomes and their development, most often on model organisms, and applied genetics, with its "utilitarian mission" of studying genome anomalies and seeking to classify genes for biomedical applications. These divisions correspond to two scientific configurations around different referents, reflecting a vision of science as producer of academic knowledge versus science as producer of economic or applied use values.

In order to link scientific advances to a development of biotechnologies, the uncertainties related to a new field, in terms of knowledge, techniques, data management, funding, and ethical questions, had to be reduced through collective forms of organisation and institutional initiatives. The public authorities thus initiated a series of actions which served as both motors and attempts at segmented co-ordination, interrelating public and private sectors. These actions were to produce contradictory effects.

1.1 The co-ordination of public and private research activity to create an S&T space

The construction of the first genetic map of the human genome corresponded to a specific configuration of players (designers, producers, users) that gave rise to its own innovation dynamic in international competition. This configuration was largely stimulated on by a private player in the non-profit sector.

1.1.1 The driving role of the private non-profit sector

An original feature of French medical research relative to the general organisation of the country's research is the role of foundations and non-profit organisations which mobilise private resources (e.g., for the Institut Pasteur or the Institut Curie). Their presence serves to modify science-State relations. In this context, genomics, emerging from a new techno-scientific field based on genetic engineering and biotechnologies, was the fruit of the decisive impetus of two private structures, the Centre d'Etudes sur le Polymorphisme Humain (Centre for Research on Human Polymorphism, CEPH) and the Association Française contre les Myopathies (French Neuromuscular Distrophy Association, AFM).

The CEPH was a private laboratory set up by a foundation in 1983; as such, it defined its own rules of operation and personnel hiring, but as of 1988, it was funded by a direct budget line from the Ministry of Research. From an *organisational* standpoint, the CEPH constitutes a double breakthrough. In terms of research, it breaks with the artisanal practices of French research teams. Its investment in a massive, technological, semi-industrial approach depends on funding for operations and equipment that is three to four times higher than that of a classic laboratory of the same size. From the *management* standpoint, its private status, which allows it to hire personnel without the constraints faced by public institutions like INSERM or the CNRS, make it an atypical structure enjoying research conditions close to those prevailing in the United States. *From the standpoint of the micro-foundations of the technological evolution of sequencing,* which extends to its present industrialisation, this double feature allowed the CEPH to situate itself in an essential segment.

The AFM is a non-profit organisation founded in 1958 to work for the curing of hereditary neuromuscular diseases. AFM's activities fall into three domains: collection and management of funds, assistance to individuals and research. In 1987, observing the relative inadequacies of the State concerning research on genetic diseases, AFM decided to provide financial support in this area. Since 1988, its scientific policy has covered the entire spectrum, from clinical to therapeutic to genetic research, with a combination of long- and short-term projects, exploration and application, in short, every activity likely to contribute to the development of treatments. Along with its scientific programmes, the AFM's laboratory, the Généthon, had two development programmes in computer science and technology.

United by common interests, the joint activities of the CEPH and the AFM set out the main significant parametres of genomics in France, a crossroads between academic scientific research and industrial applications, and related biotechnologies. Their appeal to the public authorities to create a dynamic by initiating path-breaking scientific or technical programmes perpetuated this existence and gave rise to the main dimensions of a **new scientific and technical space** permitting complementary interventions by the public authorities, public and private research bodies, industries and hospital institutions. In 1992, Généthon's publication of the physical and genetic maps of the human genome placed French genomics in the forefront in face of international competition. The success of genomics through the initiatives of the AFM, "government partner," led the public authorities to take over for the association on issues that the latter considered to be of collective interest, such as the localisation and identification of genes, and to follow in its footsteps by investing heavily in mapping and sequencing.

The AFM's schemes contributed more to creating a research field that was well endowed financially and technologically and that brought together different skills around genomics than to shifting the orientations of public research. They thus exerted a "lever effect" on the existing scientific structure, mobilising a high-level academic potential and giving rise to a technological potential for research with rapid applicability, thus creating a competitive advantage.

1.1.2 Co-ordination mechanisms between public research bodies : scientific and technical dynamics and institutional inertias

The CEPH and Généthon had opened up a scientific field by means of one technology, massive sequencing; the public co-ordinating mechanism was responsible for anchoring this technology in a specific context (a segmented scientific community) by creating an institutional framework structuring this community around shared objectives.

In order to meet this need, the public authorities set up the Groupement de Recherches et d'Etudes sur les Génômes (Genome Research Group, GREG), which was given the double responsibility of distributing public resources and developping forms of supervision for the scientific and technical activity. Created in 1993 in the midsts of the scientific (and governmental) cleavages around the controversy over whether or not to join the international genome programme, the GREG, which brought together the Ministry of Research and the major public research institutions (CNRS, INSERM, CEA, INRA, INRIA), marked the culmination of a period of political non-decisions. It was thus an institutional compromise, a stabilisation of contradictory rationales, following an expert's report establishing the benefits--scientific, technological, economic, commercial and training-related--that might be expected of such a project, at a time when Anglo-American research, supported by national programmes, was taking a decisive lead.

The effort at structuring and co-ordinating the genomics research community focussed on the development of technological advances in the area of systematic analysis of DNA and genomes (automation, identification, marking, separation), the development of the bioinformatics services that are essential to genome research and training activities to improve the skills level of GREG's partners in bioinformatics and turn out researchers with double specialities in information science and genetics.

Through the resources allocated to it, GREG had the effect of displacing a certain number of teams towards a field between the genome and medical genetics, which gave them a respectable position internationally and allowed them to benefit from the consequences of Généthon's mapping and advances. It defined the contours of a scientific community at the intersection of fields of common interests, but this community remained fragmented, without co-operative ventures.

Observing the absence of a significant technological breakthrough for the study of genomes, GREG set itself the task of compensating for this deficiency by making projects offering real technological innovations its priority. Indeed, the analysis of the low funding level of technological research (excluding computer science) between 1988 and 1993 showed a near-total absence of projects emanating from French SMEs, with the exception of the Bertin Company's Labimap project. But, for lack of proposals of adequate quality, technologies represented only 6 percent of its funding. Suspended after three years under pressure from the AFM, which, in its dealing with the Ministry, advocated a transfer of academic knowledge towards semi-industrial projects, its action was very short term and thus not determinant.

The juxtaposition and simultaneity of the mechanisms for co-ordinating public activity with the AFM on the one hand and the GREG on the other gave rise to an institutional segmentation of scientific policies for the life sciences and the scientific field in biology between medical genetics and genome research, the effects of which were negative for both scientific co-operation and the creation of biotechnologies. The mechanisms for incentives and co-ordination did not function consistently enough to create common rules and norms that might provide public action guidelines for supervising collective scientific and technical activity. Institutional inertias and an uncertain legal environment thus encumbered the institutionalisation of a potentially innovative scientific and technical space.

1.2 Difficulties in setting up a space for innovation in biotechnologies

The first CNRS document offering a forward-looking vision of biology, *Biologie 1990 - Enjeux et problematiques* (Biology 1990 - Issues and problematics, 1987), assigned biological research four major issues for the society: health, the food-processing industry, the use of micro-organisms and the environment.

Given these requisites for scientific research, we shall examine the ways that the scientific and technical space for genomics was opened to the medical and industrial sectors interconnected by biotechnologies, as well as the obstacles to such a development. Indeed, the institutional mechanisms that were put in place partly determined the way relations were organised between research and industry, and their interactions during this period. Through the new organisational forms that they gave rise to, they provided frameworks for the more or less sharp accentuation of science-industry integration and the production dynamic of the new technologies arising from the encounter of the knowledge mobilised and innovative players. But they came up against the potential constraints of the national institutional frameworks--the financial, legal and training systems.

1.2.1 Support mechanisms for opening the scientific and technical space of genomics to innovation

The opening up of the S&T arena to partnerships likely to transform scientific discoveries into economic or social values depended on public institutional mechanisms, and the AFM's strategies.

1.2.1.1 Institutional mechanisms for partnership between public research bodies and industrial research

In typical fashion within the hierarchical functioning of French schemes, incentive programmes were set up at the initiative of the Ministry, along with actions proper to the public research bodies.

Biotechnologies have been the focus of national programmes in France since the beginning of the 1980s: the kick-off "Essor des biotechnologies" (Biotechnologies expansion) programme in 1982, the Biotechnologies National Programme in 1985, "Sauts technologiques" (Technological leaps) in 1988, the Bioavenir (Biofuture) programme in 1992. Developped by the Ministry of Industry's Research and Technology Fund (FRT) and the Ministry of Research, they were eleborated in different departments of the CNRS with a double objective:

- Encouraging researchers to envision, and if need be develop the results of their work applicable in the short term, in the form of technological spin-offs ;
- Working for the development of fundamental research upstream from the biotechnologies, and in particular, furthering cross-disciplinary collaborations between laboratories.

The idea was thus to favour the applicability of research in order to reinforce links between scientific research and the creation of technologies for public or industrial research, followed by the emergence of small biotechnologies companies.
In fact, this programme, carried out in the form of Actions Thématiques Programmées (Programmed thematic activities, ATP) lasting two years, suffered from increasingly low funding (10 million francs for two years in 1983 ; 2.4 million francs in 1988) and had poor implementation (13 to 27 contracts per year).

As for the Bioavenir programme (1992-1997), initiated by the Minister of Research (H. Curien), it was originally presented as a model of co-ordination between public and private research, in terms of its scope, its duration and its wide-ranging mission. Supported by the public authorities (Ministries of Research and Industry), it involved the main public research bodies (CEA, CNRS, INRA, INSERM, Institut Pasteur, universities) in a collaboration with one quasi-exclusive industrial partner, Rhône-Poulenc. With a budget of 1.6 billion francs (1 billion from Rhône-Poulenc and 610 million from the Ministries), it was intended to ensure the mobilisation of skills and means at the interface of life sciences and chemistry and strengthen collaborations in order to accelerate the transfer of knowledge between fundamental research and applied or industrial research. But more specifically, for Rhône-Poulenc, the idea was to invest far upstream on fundamental research, to identify and characterise new biological targets in order to take advantage of the most recent developments in molecular biology and genetics and to adopt a rational conception in the elaboration of new active compounds by "generating the skills needed to overcome identified technological barriers."
For the public research bodies, and the CNRS in particular, the rapprochement of research with industry came under a certain number of programme activities initiated by its Life Sciences Department (DSV) :

- Cross-disciplinary research programmes, which involved several CNRS departments and developped interfaces with industry.
- One ATIPE programme (Actions thematiques incitatives sur programmes et équipes : Thematic activities providing incentives for programmes and teams). Between 1990 and 1994, the ATIPE programmes led to the constitution of 32 new teams at the DSV/CNRS.
- The founding of mixed units (6 for the DSV between 1986 and 1992).

1.2.1.2 Mobilisation of the AFM for the involvement of industrial support

As of 1994, the AFM refocussed its activity on gene therapy. This reorientation made it necessary for the association to acquire an industrial backing capable of creating a market to make the large-scale development of these therapies viable. The AFM relied on a double strategy. On the one hand, it signed co-ordination agreements with biotechnologies firms, once it had organised concerted actions to generate innovation by combining specific complementary assets (with the AFM monitoring the patients' genes). For the small companies in biotechnologies, the contribution of the patients' associations provided an incentive to involve themselves the field of gene therapy, through long and costly investments, through the close collaboration with clinicians and the implementation of the therapy (the co-operation of the patients), through the co-ordination of complementary assets to bring together varied knowledge and know-how (setting up a technological basis, co-ordination of research centres in vectorology and gene therapy centres, etc.), which were subsequently to allow the companies to transfer acquired competences on rare diseases in order to enter the sought-after mass markets. The AFM thus signed agreements, first with Transgène, then Genset, and finally Rhône-Poulenc. This was to give rise to the problem of the private appropriation of externalities produced through co-operation: the AFM ultimately registered patents on the genetic disease genes discovered in order to protect the pharmaceutical industry's exploitation rights.

Furthermore, alongside its co-ordination activities intended to modify research practices, by initiating ties between research teams funded by the association and industry, relations which were to be perpetuated over time, the AFM sought to influence the public authorities so that the latter would attract to the field of gene therapies the industrial skills likely to create a favourable environment for them in terms of technological platforms and market.

1.2.2 Obstacles arising from the institutional frameworks

These obstacles originate, on the one hand, from institutional factors of management and supervision specific to the biomedical sector and, on the other, from the specific French configuration of the national system of innovation.

1.2.2.1 The impact of the legal framework on the science-industry relationship in the biomedical field

The factors that might be detrimental to the development of the French industrial structure in the context of international competitiveness lie first of all in the cumbersomeness and complexity of procedures for the supervision of research and experimentation, and second in the uncertainties of the legal framework for this research-industry interaction.

In the area of *biomedical research and clinical experimentation in therapeutic biotechnology firms*, which involves the notion of the "**genetically modified organism**", the much greater national research effort required in order to go beyond the phase of clinical trials was blocked by the abundance of regulations and inconsistency of texts, as well as the intervention of multiple supervisory institutions. This institutional apparatus and proliferation of procedures, which created a veritable obstacle course for those requesting trials, proved to be largely dissuasive. Companies of sufficiently large size (e.g., Transgène) relocated their trials outside of France.

In the area of *intellectual property rights*, the organisation of closer interactions between public research and industry suffered from the constraints imposed by the acuteness of the ethical problems raised, as well as a context of dispersed, if not framented industrial property. Indeed, this situation raises the problem of the **legal protection of biotechnical inventions** and the **patentability of the elements and products of the human body**, insofar as the latter constitute, for the moment, the essential source of "raw material" for biomedical research and industry.

In the United States, the need to describe the new function of the genetic sequence claimed as an "invention" led to a maximum of anticipation, with requests for the protection of the widest possible range of potential applications. European legislation, on the other hand, did not ratify the principles established by the changing technical practices of the European Patents Office until July 1998, when the draft directive of 1988 was definitively adopted.

European patent law thus became more homogeneous by successive steps in the direction of a technique-based law permitting greater interaction between research and industry.
But during the entire debate over the community directive, which coincided with the first phase studied here, the biotechnologies players came up against the uncertainty of the legal framework.

The *status of the procedures and products of gene therapy* has also constituted an obstacle to the development of the biomedical industry in France.
Gene therapy involves procedures that must meet norms on medical devices (e.g., quality controls and insurance). In this area, the singular nature of the French institutional mechanism within the European Union, which aroused the opposition of the SMEs in the biomedical sector until 1995, penalised biomedical R&D and weakened existing ties between research and industry in France. It thus led the French biomedical industry either to abandon research projects or to relocate clinical trials and the manufacture of medical devices outside the country. This particular feature only came to an end with the application of the European system (CE marking rules since 1998), which improves upon the previous French legal framework.

With regard to the products of gene therapy, their status (drug or other) still remains uncertain. Such a definition is important for the distribution of negotiating powers and forms of co-ordination between the different players in research, health institutions and industry. Uncertainty over the development of these products, and the conditions of sharing the results of scientific inventions can play a dissuasive role in industrial development and influence firm strategies.

The economic incentives of government action in France over the period studied seem to have been too little and too late to encourage co-operation by giving rise to the creation of small French enterprises, while regulations remained too cumbersome.

1.2.2.2 The impact of other institutional forms of the national innovation system

Two "societal" forms can be identified here, one arising from the financial system, the other from the educational and professional dimension.

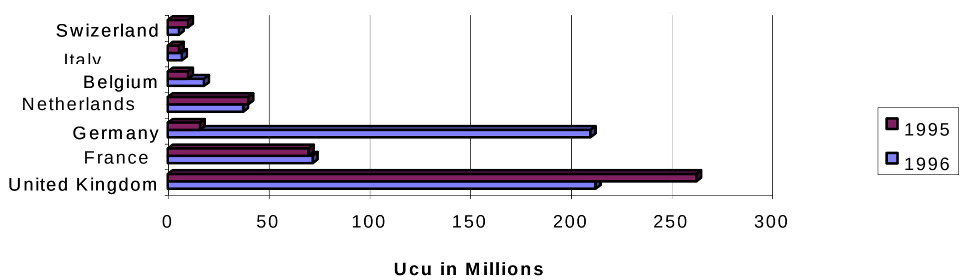
On the first point, the financial, fiscal or legal obstacles to the creation of start-ups that are most often cited include :

- The disadvantageous tax status of stock options issued by the new biotechnologies companies ;
- the questioning of immediate restoration of the research tax credit for the new high-technology companies ;
- the absence of a system of appropriate funding, start-up funds and venture capital ;
- inadequate registering of patents by public research bodies with exclusive licenses for small enterprises. (In fact, venture capital only invests in patented technologies, and the competitors register patents.)

Unlike other countries, moreover, there is no satisfactory legal solution for the establishment of consortiums bringing together small and large companies and laboratories for the development of joint technological resources or co-operative research centres.

The relevance of some of these arguments is, however, open to question. Concerning the lack of funding, even if, out of the two hundred investment companies in France, less than a dozen invest in start-up technologies, there were, besides the ANVAR, French venture-capital funds with growing assets. In 1995, biotechnologies concentrated 15 percent of venture capital (174 million F) in France, and the medical-healthcare sector, 18 percent (260 million F) (Source: AFIC). This rate was subsequently to show a very sharp increase.

Figure 5 : Venture capital investment in biotechnology and health care by country



Source : European Venture Capital Association

Thus, the bottleneck is not to be found in the financial resources. For Pascal Brandys, president of Genset, "The main obstacle to the creation of biotechnologies companies remains the lack of quality entrepreneurs".

In the educational and professional sphere, the obstacles identified include :

- a rigid definition of the researcher's status, which excludes any participation in the capital of a start-up and would create difficult conditions of return to the original public research institution ;
- the absence of interrelated scientific and entrepreneurial training programmes.

In fact, the main obstacles seem to arise from specific practices of the public-sector researchers, who aspire to an academic scientific career where criteria for success and the corresponding incentives are established within a scientific community fashioned for the production of scientific knowledge according to a dominant "order". Technological research remains little developped because it does not advance a researcher's career, nor does it contribute to advancement in industry or mobility towards the companies. As a result, public-sector researchers, who are the privileged intermediaries of closer ties between the S&T and industrial spaces, through the transfer of ideas, skills and technologies, enjoy very little mobility towards the companies. It is symptomatic that the qualitative leap made in France through the introduction of large-scale sequencing techniques came from a private laboratory (Généthon) and was viewed amongst biologists as a "technological excess" to be associated with development rather than research.

1.2.3 Little efficiency in terms of technological performances, innovation and competitiveness

Beyond the rhetoric developped by the scientific units of the S§T institutions about the opening up of research to the socio-economic players and the strengthening of industrial partnerships, the results of the interaction of French institutional arrangements for the development of ties between life-sciences research and economic performances, technological opportunities, creation of new activities and industrial development remain limited.

According to OST [2]data, France's position is better on the scientific level (publications rating) than on the technological level. This gap can be illustrated through three indicators: patents, contractual relations between public research bodies and companies and the creation of companies on the basis of scientific potential.

On terms of patents, the same decline can be observed in biotechnology as in other fields, with the result that France accounted for only 6.4 percent of European patents in 1996 (6.6 % for the pharmaceutical industry). For American patents, the decline was less pronounced in biotechnologies and the pharmaceutical sector (5.1 %), reflecting the implantation of French firms in the United States during that period, through the creation of subsidiaries or the acquisition of American companies. In all, biotechnologies represented 2.9 percent of French and European patents and international patents designating France in 1996.

In a context of limited co-operation between public research bodies and business, the particular features of relations between academic research and companies in the life sciences can be identified (cf. Table). According to the White Paper on R&D co-operation between industry and the public sector published by the Syndicat National des Industries Pharmaceutiques in 1997, network relations function with INSERM and the university hospital sector on collaborations for clinical research. At the CNRS and in the universities, interface structures aimed at optimising relations with industry are insufficient, or overly centralised. When the rationales of the two kinds of partners do not converge--which is most often the case--no attempt is made to bring them closer in order to formalise the mutual benefits of a long-term collaboration.

[2] Observatoire des Sciences et des Techniques

Relations : industries life sciences – public organisms

Organisms	Research Services	Contracts	Outlook for Industry
CEA	- synthesis of biological molecules by stable and radioactive isotopes - pharmacological and pharmacokinetic studies for preparation of AMM reports - validation of bioindustrial processes for their capacity to destroy unconventional infectious agents (prions)	114 contracts in 1994 : 45 % for collaboration (average length : 2 years), 5 % research services Total amount : 32 million F (RP-Rorer, Sanofi, P. Fabre, Servier, Biotech, Orion, Glaxo, Basf, Roussel-Uclaf, Transgène)	The CEA wants to be more officially involved in industry's decision-making bodies. Industry has the same desire, with the hope that this involvement will be reflected in the laboratory experiences.
INSERM	- delegated research (exploratory phase, pharmacological targets, molecular screening), financed by industry - shared research (new medications) - integrated team - research services	Unavailable	Need for more profound collaboration. Reciprocal recognition of diplomas facilitating both mobilities and careers via mixed jobs.
CNRS	- 5 mixed research units in direct relation with industry - framework agreements with individual contracts - participation of Life Sciences Dept. in Bioavenir programme - short-term contracts - human resources support	The CNRS prefers the formula of mixed units over research contracts	Favouring closer ties between public units through the development of unifying themes. Reciprocal recognition of diplomas facilitating mobilities and careers via mixed jobs.
Universities	20 post-graduate diplomas (DEAs) in "medications" fields including: - pharmacologically active substances - evaluation of medications and xenobiotics - pharmaceutical legislation	Unavailable	Improved visibility of research training programmes. Integration and organisation of doctoral programmes. Encouragement of mobility (review of status).
Pasteur	- bacteriology and mycology - virology - biochemistry and molecular genetics - biotechnologies	The office of development and industrial relations ensures the transfer of results from the units towards the industries (22 million F for expertise in 1994, 5 million F in R&D contracts, 200 million F in licensing fees paid to the institute.	Opening up the institute's collaborations (two privileged partners : Sanofi Diagnostic Pasteur, Pasteur Mérieux Sérums et Vaccins)

Source : Livre blanc de la coopération en R&D (SNIP, 1997)

This situation explains why all the technological methods of molecular biology were developped in the United States and Great Britain, with French researchers depending on US companies or their English subsidiaries (Molecular Dynamics, Amersham) for 80 percent of the equipment and reagents used, as well as for computer software. France now has to make up for its backwardness in **platform technologies.** Scientific advances in vectorology in France, for example, have not given rise to the creation of companies. The most revealing recent example is that of the technological change in DNA chips, which, spreading through their miniaturisation, were to revolutionise sequencing and detection of pathologies. This shift could have been taken place in France at the beginning of the 1990s (the skills existed), but the idea was exploited by the California company Affymetrix.

Similarly, research in **gene therapy** was deemed "rather well developped" in France in the SDV economic report of 1992, with several first-rate teams on the international level, but the lack of ties with the pharmaceutical industry slowed down the development of the necessary biotechnologies. In mid 1996, there were a few dozen patients being tested in France, compared to 1,230 in the United States, 61 in Great Britain, 55 in the Netherlands and 47 in Germany.

The creation of businesses has thus remained slight, while biotechnology is a sector where innovation emerges above all from small companies, whose creation is closely tied to the institutional system. In terms of performance, Europe's lag in 1996 relative to the United States in the area of biotechnologies companies was patent (716 companies, employing 27,500 individuals, compared to 1,287 in the United States with 118,000 employees, according to Ernst & Young), but the industry was getting off the ground. France, however, wound up in third place in 1997, behind Great Britain and Germany, countries where recent changes in legislation and the commitment of public authorities have given rise to the doubling of the number of companies every year since 1996. In France in 1996, fewer than fifty start-ups had arisen from research spin-offs, often with ANVAR's aid for innovative projects. Several of these have risen to world rank (Genset, the first to have been rated on the new market and NASDAQ in 1996, Cerep, Flamel Technologies, IDM, Appligène, Oncor, Transgène, Genopoïetic, Chemunex, Biovector Therapeutics). But with the patrimonial rationale winning out over the entrepreneurial one, few small companies coming out of the academic world became growth enterprises. The oldest one, Immunotech, a 1980 spin-off of INSERM's research on monoclonal antibodies, managed to place itself on the market but was bought out by the American Coulter group in 1995, under pressure from venture capital companies.

Following the collapse of funding from venture capital companies and investment funds after 1992, the *strategies of companies specialised in biotechnologies* (CSBs), consisted to forming multiple alliances with the major pharmaceutical groups. For more than twenty years, the biotechnology products sector has been dominated by the US industry, which held 90 percent of the world market in 1996. Two-thirds of these markets are oriented towards therapeutic and diagnostic products. After the first generation of biomedications resulting from genomics--human proteins with therapeutic functions, the sale of which in the United States represented nearly 25 billion francs in 1994--a second generation emerged from the effects of sequencing and the isolation of genes implicated in diseases. In France, meanwhile, this potential market segment saw the creation of partnerships among research units, biotechnology companies involved in the identification of genes and regulatory regions associated with diseases and the pharmaceutical industry (with or without exclusive licenses), but these most often involved Anglo-American partners. Genset, the leading French genomics company, had exclusive agreement protocols for a single disease with two pharmaceutical groups, Synthélabo and Johnson & Johnson. Génopoïetic developped gene therapy techniques on the basis of patents from the Institut Pierre et Marie Curie, with support from Rhône-Poulenc for product marketing. And Transgène was essentially created with public and charitable funds and later, for a limited period, with support from Rhône-Poulenc (prior to agreements with HGS and Schering-Plough in 1998).

In spite of government efforts for the *funding of industrial R&D* (according to the MENRT, public authorities allot over 10 billion francs annually to biological, agricultural and medical research), two paradoxical elements emerge: on the one hand, the French industrial fabric's low capacity for integrating the advances made in the S&T arena, and on the other, the know-how of a small number of industrial groups for profiting from public funds and resources allotted to research transfers towards industry and the development of industrial research.

On the first point, we have observed the inadequacies of industrial development of technological advances for research, notably the technological platforms. The second point relates to the concentration of public funding (cf. OST) in a small number of sectors and the predominance of several large industrial groups as beneficiaries of technological policies and public subsidies for R&D.

The interministerial Bioavenir programme (R&D for the integration of concepts and innovative techniques in biology) is representative of the French policies of major technological programmes shaped by the Colbertian model of the post-war period. It has monopolised public funds instead of using them to encourage an industrial fabric of small biotechnology companies, and, contrary to the aims of an umbrella mechanism, has compartmentalised its collaborations.

1.3 Evaluation of the innovation dynamic of institutional frameworks for the 1985-1996 period

At the level of the *scientific and technical system*, several strategies for action have been superimposed, without necessarily resulting in convergence among them.

The CEPH and AFM, which private structures, have played innovative roles by introducing semi-industrial scientific methods into molecular biology and developping molecular genetics. They have laid down the foundations for a new scientific and technical space and given France international standing in genomics.

The GREG, as a framework for controversies, negotiations and elaboration of compromises between the different public Public S&T institutions and the university hospitals, was the prefiguration of an initial rapprochement of teams from different disciplines and outlooks. Its intermediary role permitted the initiation of a collective organisational learning process, but one that was limited to the scientific environment. It did not serve as a magnet for structuring a broader space around a clearly identified national genomics programme bringing science and industry into interaction.

The Bioavenir programme, meanwhile, has had an impact on the socialisation of public researchers to industrial research by showing them that it was possible to conduct fundamental research on industrial preoccupations.

For the *educational and professional system*, the consequences of the schemes for public-private co-ordination have been segmented and have not allowed the creation of a cross-disciplinary dimension essential to this zone of innovation, with a "professional space" transcending the fields and missions of the different public or private research institutions and bringing together scientific, technical and applied knowledge and skills. The continued compartmentalisation between institutions, the inadequate hybridisation of disciplines (e.g. for bioinformatics), and the tendency towards dispersal of the means of sequencing (or preclinical tests for gene therapy) in isolated sites of "artisanal" research have all slowed down a circulation of "contextualised" knowledge about the analysis of genomes, its socio-economic stakes and the technological means to be mobilised in order to participate internationally in the production of the data conditioning their utilisation.

At the level of *State action*, the interventions of institutional players have been discontinuous and out of phase with the dynamic that globalisation has given to strategies of innovation and industrial diffusion in this field. France has not been the driving force at European level that its scientific base might have permitted. The unsuitability of the public S&T institutions' information tools, the sporadic nature of public action owing in particular to the political instability and tensions between the Ministry and the different public S&T institutions in the games of influence and competition amongst criteria (medical advances, genes of economic interest, etc.), the absence of any real evaluation of discontinuous schemes and inadequate procedural training--the characteristics of a top-down public policy--ultimately had a disturbing influence on the creation of a space for innovation in genomics by a private player called upon to compensate for the failings of public action.

The process of building this new field, genomics, thus remained fragmented, for lack of an institutional awareness that would have significantly changed the public authorities' forms of intervention. This sectoral public policy has in fact been marked by a "determinism" of institutions shaped to meet objectives defined by post-war scientific and technological policies (Callon and Foray 1998). Its "mission-oriented policy" (Ergas 1994) characterised by a centralisation of top-down decisions and a concentration of resource allocations on major programmes) has been juxtaposed with zones of non-decisions and dispersion over the new fields to develop in a science-innovation tandem. In addition, it has remained bound to the linear model of innovation that goes from basic research to applied research to the development of products or services. In the French industrial environment of the 1985-1996 period, it has thus generated low efficiency relative to the stakes of the mechanisms intended to produce, distribute and exchange new knowledge and skills.

2 INSTITUTIONAL REFORMS AFTER 1996 : THE INSPIRATION OF THE ANGLO-AMERICAN INNOVATION MODEL REAPPROPRIATED ON THE BASIS OF FRENCH INSTITUTIONAL FEATURES

At the same time that the institutional structures, backed up by the major player that the State represents in France, were outlining the operation of private and public R&D activities in the area of genomics, certain institutional arrangements were modified under the impetus of other dynamics. Indeed, scientific and technological interdependencies and dissemination in terms of the globalisation of research in this field not only modified basic techniques, and in parallel, the organisational forms of the different sectors involved, but had as its corollary the generalisation of an optimal "model" for the production of science and innovation. In France, this model had the concrete effect of colliding with the Colbertist model of the science-innovation tandem but did not replace it, insofar as the overlaps themselves had structuring effects.

2.1 An "ideal model" of coproduction of knowledge and science-industry interaction in biotechnologies

2.1.1 Origin of the model

Molecular biology developped in a transnational space, but its rapid rise is tied to the major role played by the United States and the significant investments allocated to its development by public bodies as a follow-up to funds previously provided by private bodies such as the California Institute of Technology or the Rockefeller Foundation (Morange 1995).
With the spread of genetic engineering at the end of the 1970s, contemporary molecular biology became more technical and more oriented towards a development of its applications. Most of the projects and investments were concentrated in the United States. The accelerated growth of this techno-scientific field then amplified existing features of the development of the sciences after the Second World War. Open-market competition became an essential criterion for political and economic activity, and this political transformation was accompanied by a corresponding expansion of scientific practices connected to production

spaces with economic and/or social value and a growing interpenetration between academic knowledge and the search for efficiency. This evolution led to a phenomenon of hybridisation between scientific, technical, industrial and financial activities, depending on particular modes of production and transfer of knowledge, in scientific-industrial concentrations exemplified by Silicon Valley or Route 128.

The emergence of this "new" regime for the production of knowledge has been described by Gibbons in positive terms for the stakes of political action, economic dynamics and scientific development ("The New Production of Knowledge, the Dynamics of Science and Research in Contemporary Societies" in Gibbons et al 1994). In the academic literature, it became known as the "Triple Helix model", advanced notably by Etzkowitz and Leydesdorff (1997).
According to this model, the locus of what now evolves towards a "coproduction" of knowledge is situated at the intersection of three interacting institutional spheres: the university and the research bodies, industry and the public authorities. The aim of this interrelationship is to develop research capacities and a transfer of economically relevant knowledge to industry by integrating the research infrastructures in the innovation systems. The underlying hypothesis of such an approach is that the economic dynamic is now based on the development of generic knowledge and its diffusion within the fabric of the production apparatus. In this setup, the interventions of the public authorities should thus tend to favour a virtuous spiral between the multiple linkages of cross-over networks that emerge at the different stages of the innovation process. By formulating policies and programmes encouraging strategic alliances between companies and research organisations, the creation of spin-off firms, the implantation of R&D structures transcending traditional institutional borders (public-private, academic-applied, etc.), the founding of scientific and industrial concentrations at the local level, and so on, these public interventions would follow a rationale aimed at the organised accumulation of knowledge and the creation of capacities for innovation.

2.1.2 Transfer of the "model": adoption as a normative system and reinterpretation according to each country's specific institutional contexts

The discourses related to this model were linked to expanding practices of research production that were nonetheless tied to the institutional context of the United States. These practices were transformed into a normative system on the basis of the shared representations made by the institutional players, and this system was then drawn upon in order to create new shared socio-cognitive guidelines for public action, as criteria for updated forms of action but with different kinds of appropriation depending on the European countries involved. It was spread largely through experts' reports and programme activities, mainly those of the European Commission. Interaction with R&D at international level and competition/co-operation with other systems of research and innovation gave rise, at the European level of institutional support, to the diffusion of scientific advances and techniques, the standardisation of tools and procedures, the modification of guidelines for the science-innovation relationship and the aligning of European intellectual property law with American law in the biotechnologies field. Given the not inconsiderable volume of funding provided by the European programmes relative to French budgets for research or technological development outside the major programmes, the impetus provided by the European dynamic could help to restructure the functioning of public and private research in France. In particular, the emphasis placed on co-operation that is not only transnational but also transdisciplinary and transorganisational (in the sense of a greater integration between science and industry), as well as the replacement of a rationale of funding alone by one of incentives centralised at European level, which are the priorities of Community action, seek to strengthen the bases of a mode of research organisation that is more open to economic applications (multiplication of partnerships and dialogue between decompartmentalised fields of research and action). The latter is considered more efficient according to the current requirements of international competitiveness. The quantitative extension of the practices privileged by these programmes could lead to a qualitative change in the overall research system. Beyond stimulating the dissemination of knowledge between member countries, these policies tend in fact towards effects of normalisation in the production of knowledge and the creation of technological and organisational standards that can be linked to the diffusion of the updated "model" of the mode of production of research at work in the biotechnologies.

Such irreversible processes and the disruption of representations in France are bringing about an endogenous societal reaction of adjustment to the globalised environment, a change in the guidelines and the forms of public action. This results in an institutional dynamic consistent with the scientific and technical dynamic, and the creation of conditions at local, national and international levels that allow "transforming research results into economic and social innovation".

2.2 The beginnings of new forms of public intervention ("diffusion-oriented policy")

At the level of State action, a certain number of programmes and new measures, of general or particular scope, have permitted the introduction of new strategies for action by removing legal obstacles and created conditions for the development of small innovative enterprises through the shift from a patrimonial to an entrepreneurial rationale.

2.2.1 Innovation-promoting changes in the institutional environment

The law on innnovation of July 1999 was explicitly aimed at bringing public research and companies closer together in order to "increase the capacity for innovation and the creation of wealth". It allows for several forms of incentives :

- The elimination of statutory restrictions on researchers' mobility, allowing them to create a company on the basis of their studies without definitively leaving public research, or to contribute their expertise or their participation in the capital of a company while maintaining their posts.
- The creation of structures favouring the emergence of innovative small enterprises, notably spin-offs from research institutions or universities: **incubators** offering an implantation site but also technical support and legal and financial advice, and **seed-capital funds** to facilitate the first stage of creation, with State funding leading to calls for projects as well as a competition for aid in the creation of innovative technological enterprises.
- The institution of a fiscal context favourable to subscription funds for shares in the creation of enterprises (FSPCE, employee profit-sharing) and joint funds for investment

in innovation (FCPI). The tax system for stock options remains largely dissuasive, however.

- The inclusion of innovative small enterprises in a legal framework that is more appropriate to them: the simplified stock company (*société par actions simplifiée*, SAS), which facilitates calls for investors and venture capitalists.

In terms of the *financial system*, a positive change emerged with the creation of the New Market and EASDAQ, allowing high-tech companies to be rated on the stock market. This trend was accentuated by the State's creation of a public venture-capital fund of 1 billion francs which, through the lever effect, allowed several times this amount to be raised amongst institutional investors, banks or local communities.

2.2.2 A new technological policy for the biotechnologies : bridging between public research and biotechnologies

Since 1996, the life sciences and biotechnologies have been made priorities for interministerial governmental action, in order to strengthen France's position on an essential strategical issue for growth and employment. A second Biotechnologies Programme was undertaken for five years, with joint public-private funding of 1 billion francs following calls for proposals. Its objectives are to stimulate collaborations between public laboratories and SMEs, to aid in the development of innovative principles or procedures (with the goal of tripling the number of international patents registered by the French), to favour the emergence of several thousand CSBs in order to create four hundred stable high-tech companies and set up new biotechnologies sectors that create jobs.

In 1998, the Ministry of Research, which is empowered to intervene in industrial support for research, launched appeals to promote actions between public research and SMEs along two main lines: transfers in biotechnologies, where the large majority of the projects selected deal with health (genomics, diagnosis and gene and cell therapy), and health technologies (instrumentation, imaging, bioinformatics). In 1999, funding incentives were focussed on programmes dealing with the extension of human genome sequencing and targetting therapeutic security and new treatments, functional genomics and biomaterials. The Ministry of Industry likewise launched a call for projects in "post-sequencing genomics" along three bio-industrial tracks related to predictive, preventive and therapeutic medecine and thus giving rise to a partnership between public research, small biotechnologies industrialists providing technologies and services and applications CSBs.

Apart from incentive-providing grants, the State's impetus is now channeled in two main directions. The first involves the creation of genomics infrastructures: major facilities like the Centre National de Séquençage (which has a public budget of 80 million francs for ten years), the Centre National de Génotypage (50 million francs annually), the Centre de Ressources Informatiques Infobiogen and the Centre de Ressources for DNA collections, along with the development of national networks of genomic bioinformatics and genopoles. The second involves umbrella research programmes.

The most state-led ministerial scheme for bringing together in one site research (public, private, industrial), small enterprises in the making, experienced CSBs, industry and the university is the genopole for genomics and biotechnologies implanted in Evry in 1998. The idea is to develop a European-level pole of some sixty biotechnologies companies around the massive facilities of the CNS, CNG, and AFM laboratories by drawing on the results of public research, the installation of new companies in incubators and the synergy amongst research, technological platforms and industry. The project enjoys support from the major public players (State, public S&T institutions) and regional and local authorities, as well as the presence of experienced private players such as the AFM, Genset and Rhône-Poulenc-Rorer's Core Genomics Centre.

It is clear that the structural elements of the national system of innovation have been modified and that new forms of public intervention, inspired by "diffusion-oriented policy" in their principles, aim to meet the new historical objectives by replacing the Colbertian model with more diversified and decentralised conditions of innovation spread throughout the economic and social fabric. Through the multiplication of partnerships, these allow for different fields of application (agricultural and agro-industrial, pharmaceutical, medical, environmental) where the generic products of genomic research can be accommodated. They also seek to favour the strategy of incentives over that of grants in order to reinforce the fluidity of the science-industry relationship in the configuration of players relative to the public authorities-industry relationship.

2.3 The adaptation of the science-innovation pattern to the French institutional context

In concrete terms, the new institutional arrangements have to remain functionally compatible with the overall configuration of research, industry and public intervention as it has been historically defined. This means that in France, the adjustment to the "model" is subject to transposition in its application and obstacles in the necessary collaboration of its different partners.

2.3.1 Transposition of the application

The emphasis of State action on procedures such as calls for projects or competitions, which tend to stimulate the main players of biotechnological innovation, destabilises the top-down organisational coherence of earlier technological policies, which was guided by an efficiency specific to the implementation of major national programmes. The result is a combination of contradictory elements in the functioning of these procedures, through the preservation of centralised decision-making and top-down management in schemes initially designed for scientific and technical diffusion at the base. Thus, State funding is tied to a "seal of approval" bestowed on the incubators, genopoles and technological platforms by the Ministry of Research, which defines their key players and operational features. Networks are predetermined at a national scale, with certain cities "chosen" in an initial phase of the scheme: the genopole network is supposed to be federated around the Evry Genopole, deemed to be the "network head", like a "national champion" serving as the public authorities' sectoral interlocutor. These attempts at supervision run counter to the organisational configurations emerging locally at the initiative of the key players in innovation (the "intermediate institutions" of transfer), often with the support and involvement of local and regional authorities. The incentive-providing actions become focussed on forms of co-ordination imposed by a "mission" where the State would once again replace the localised autonomous initiatives of the public and private players without giving the different biotechnopoles the time to prove their effectiveness before selecting certain ones for more important roles.

2.3.2 Limitations owing to the configuration of the French pharmaceutical industry : inadequate industrial support for the biotechnologies

Access to the human genome has marked a profound break in the pharmaceutical research paradigm. The accelerated advances in molecular genetics, owing to semi-industrial, robotised approaches, are revolutionising the diagnosis of hereditary diseases; they are likewise modifying the classic schemas of the comprehension of acquired diseases and opening the door to new therapeutic strategies of gene transfer ex vivo or in vivo, commonly called "DNA medication". At this biotechnological turning point, the pharmaceutical industry has to modify its strategies according to two principles: the establishment of a critical scale and linkage with life-sciences research and the CSBs in order to integrate the methods and advances of the biotechnologies. This imperative accounts for the groupings and restructurings of industrial firms at world level (with a decrease in the number of their active patents), and their multiple forms of partnerships, in the United States, Great Britain and, more recently, Germany, with small biotechnology companies or research structures to handle innovation, namely the different steps of the development of the invention of a new medication, from the discovery of the active compound through preclinical and clinical trials to the final commercialisation.

Upstream, over the past fifteen years, one-third of the new drugs have been discovered through the identification of targets in the genome. Downstream, the economic stakes of biotherapeutics are considerable, with industry's estimates for the field of cytokines alone indicating a world market of $3 billion in 1997, while forecasts on DNA medication all anticipate some 300 billion francs by 2010 (equivalent to one-third of the present world market for etical pharmaceuticals), 20 billion francs of which would go to France.

In the United States, most of the recombinant proteins (about 70 %) have resulted from research spin-offs and been subsequently commercialised by the major pharmaceutical groups. This start-up dynamic in the biotechnologies may be explained by several factors :

- The new technological skills mobilised through the advances of molecular biology have not been anticipated by the major pharmaceutical companies, who show great inertia because of the difficulty of acquiring innovative practices owing to their overly rapid turnover.

- The replacement effect : the incentive for an existing company is less than for the later arrivals, who have new opportunities, whilst the elders would be creating competition for their own products.

These factors shed light on processes in the United States whereby the innovation process upstream is broken up into a plethora of small research companies which are sometimes absorbed because of financial obstacles (the example of Genentech, world leader in recombinant proteins, bought up at 60 % by La Roche-Hoffmann in 1990, is often cited), while downstream there are concentrations and network co-operations through share-holdings by the major groups and every imaginable kind of partnership.

France, which had a first-ranking position in medications, has suffered a considerable loss of competitiveness over the past twenty years, with the last major therapeutic groups coming from abroad and especially the United States. If the commercialisation of new compounds is taken as an indicator, France's decline is marked by the passage from second place worldwide in 1974 to seventh in 1994 (Barral 1995). In the area of industrial production of recombinant proteins, it suffers from considerable backwardness, which reflects the inadequacy of the fundamental research in the physiology of these proteins but also the weakness of French pharmaceutical companies' investment and their integration of the latest scientific knowledge in order to achieve the neccessary technological leap. In fact, companies position themselves competitively in function of their ability to develop collaborations, with academic research upstream but also with small biotechnology companies to absorb their specific skills. At the same time, they guarantee these companies commercial outlets, and their financial contributions or contracts provide funds necessary for the pursuit of their research. Indeed, there are very few CSBs which achieve a critical size and profitability without relying on major pharmaceutical groups.

In terms of structure, the French pharmaceutical sector is fragmented, with a small number of major groups, recently internationalised and in the process of restructuring, and many SMEs that are not capable, internally or externally, of assuming the R&D efforts necessary for a technological breakthrough. In terms of organisation, the French groups have mainly established ties with academic research. But the Bioavenir programme has been criticised as a means of channelling public resources (both financial and scientific) into a private industrial group. The latter, with its publicity about its gene therapy programme, presented as an integrated activity mastering the entire chain from research to production and future commercialisation, has, through its monopolistic position, indirectly blocked the development of small "artisanal" gene therapy centres in the university hospital centres and dissuaded public policy-makers from supporting the creation of small biotechnology enterprises coming out of academic research. In addition, Rhône-Poulenc-Rohrer, in the context of an R&D strategy that is now international, finally externalised its technological developments of gene therapy to the United States in the Gencell network.

The French advantage of a therapeutic "specialisation" (Casper 1999) of biotechnologies, initiated by the AFM's research activity and supported by the needs for a potential for high-level clinical research in gene therapy, thus came up against the obstacle of a lack of involvement on the part of French industry. With the same strategy of externalisation, moreover, French companies have privileged ties with American CSBs since the 1990s. They generate very few start-ups in France, unlike the computer sector, and establish few collaborations with existing companies (Transgène, Genset, etc.). This absence of relays for the development of the French biotechnologies leads the latter to sign joint-venture agreements with foreign firms, with the long-term risk of relocation in proximity to their partners.

In the absence of this linkage, although the public policy-makers and companies have integrated the institutional dimension of diffusion mechanisms, there is no "quasi-natural" continuity, like that of Anglo-American sites, between institutions producing knowledge, small companies producing skills and industries producing industrial development, the fruit of converging strategies.

CONCLUSION : INNOVATION SYSTEM PERFORMANCES IN THE BIOTECHNOLOGIES AND LEARNING PROCESS

On the level of performances, Europe's lag behind the United States in biotechnologies companies is diminishing: Ernst and Young's 1999 survey confirms the European upsurge (1,178 companies and a total of 45,823 employees, compared to 1,287 companies with 153,000 employees in the US). After a belated takeoff, two years behind Germany, France has entered a phase of structuring and maturation of its innovative biotechnologies. It now has 140 companies (compared to 220 in Germany and 280 in the UK), employing some 3,000 individuals for a turnover of 600 million francs and a research budget of 1 billion francs. Three companies are listed on the stock markets, with Genset (genomics) and Transgène (gene therapy) ranking fifth and eleventh, respectively, on the capital markets (Ernst and Young 1999).

The public authorities' commitment to promoting programmes and the improvement of the overall institutional framework have stimulated the dynamics of the "sector", as can be seen from the creation of some twenty new companies in 1999. Eighteen incubators have come into being throughout the country with 107 million francs' support from the Ministry.

Despite the worldwide decline in biotechnologies investment (their stocks underwent a 50 % drop in 1998-1999) because of competition from the information technologies, venture capital has maintained its contributions to European biotechnology companies, notably those oriented towards pharmaceutical applications. Nonetheless, no pharmaceutical product coming from the biotechnology companies has yet arrived on the market in France; the first British product was released in 1999.

On the institutional level, the presence of mission-oriented elements in the new schemes raises the risk that the State will replace initiatives by the main protagonists in the science-industry partnerships, which are beginning to proliferate under the favourable influence of general diffusion-oriented measures. Rather than seeking to dictate the downstream phases of co-ordination between public research, emerging companies and industry, where decentralised "intermediate institutions" supported by local communities would facilitate the transfers, the State should concentrate its interventions on the upstream stages. In this way, it might provide incentives for innovation processes, notably via :

- a more stimulating financial focus on research programmes on genomics and its biotechnological applications and the new training programmes needed,
- funding for company incubation before the arrival of venture capitalists and investors, which would permit more flexible projects through the mobility of potential creators and the recombination of resources,
- a tax system for stock options that does not penalise young creators and thus discourage their relocation.

On the level of public-policy organisation, examples from abroad, notably Anglo-American and German, show that the coherence of the public policy-making, its impetus-giving role and its continuity for the development of biotechnologies are facilitated by the co-ordinated involvement of certain major public players. In France, the stratified accumulation of ministerial or interministerial commissions and committees is due to be replaced by an agency-like structure for dialogue; this body would rely on the Life Sciences Co-ordinating Committee created in September 1999 for the strategic aspects of scientific policy and would work closely with the professional institutions of the biotechnologies, the pharmaceutical industry and the financial investors for development issues.

The stages of an innovation process are not linear; rather, they overlap and interpenetrate, producing a "cumulative irreversibility" because of incremental innovations. In spite of the present combination of partially contradictory institutional schemes for the development of a biotechnology sector, France has thus entered an institutional learning process.

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